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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,164	06/22/2001	Paul O.P. Ts'o	212241	9080

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CELL WORKS, INC
6200 SEAFORTH STREET
HOLABIRD BUSINESS PARK
BALTIMORE, MD 21224-6506

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,164	TS`O ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-29 and 64-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-29 and 64-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/11/02, 10/30/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

VL

DETAILED ACTION

Election/Restrictions

Applicant election with traverse of Group (iii) SEQ ID NO: 29 and the species A-L-P conjugate wherein A is YEE(ahGalNAc)$_3$, L is SMCC and P is SEQ ID NO: 29 in the reply filed 9/22/03 is acknowledged. The traversal is on the grounds that searching the three nucleotide sequences would not create a serious search burden. The arguments are acknowledged but not found persuasive because the sequences are considered to be unrelated since each sequence claimed is structurally and functionally independent and distant for the reasons set forth in the Restriction requirement filed 07/08/2003.

The restriction is still deemed proper and is therefore made FINAL.

Status of Application

Claims 1, 2, 4-29 and 64-73 are pending in the application and are currently under examination. Claims 3 and 30-63 are cancelled.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

In the instant case, the priority date granted to claims 1, 2, 4-16 and 64-68 is 11/22/1996. Claims 1, 2, 4-16 and 64-68 do not receive the benefit of the earlier Provisional application 60/007,048 because claims 1, 2, 4-16 and 64-68 are not supported by the specification and claims

of the previously mention application. The Provisional application 60/007,048 disclose a chemically uniform conjugate of formula A-L-P wherein A represents an attachment group, P represents a biologically active pro-drug and L represents a bifunctional linker. Although 60/007,048 discloses a conjugate with the formula A-L-P, the disclosure of 60/007,048 do not disclose that A represents a hepatic ligand that specifically binds to a hepatic receptor and that P represents a biologically stable oligomer that binds to a hepatic pathogen. Further, 60/007,048 does not disclose the pathogen is a hepatic virus, a liver parasite, the hepatic virus is hepatitis B, C or D virus. Provisional 60/007,048 also fails to disclose the oligomer binds to a an RNA preS1 open reading frame, the oligomer binds to surface antigen wherein the surface antigen is a core antigen of hepatic virus, the surface antigen is a S-gene antigen, or the surface antigen is a C-gene antigen. If Applicant has support for above mentioned claims, then Applicant should point out, with particularity, support for claims 1, 2, 4-16 and 64-68 of the instant application.

Further, the priority date granted to claims 17, 69, 71 and 73 is 03/31/1999. Claims 17, 69, 71 and 73 of the instant case 09/888,164 do not receive the benefit of the earlier filing date of the following applications 08/755,062 and 60/007,480 because claims 17, 69, 71 and 73 of the instant case are not supported by the specification and claims of the previously mentioned parent applications. The parent applications, 08/755,062 and 60/007,480, disclose a construct comprising a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P represents a biologically stable oligomer that binds to a hepatic pathogen. Although the parent applications disclose a construct comprising an oligomer, the disclosures of the parent applications do not disclose the oligomer comprising SEQ ID NO: 29. If Applicant has

support for above mentioned claims, then Applicant should point out, with particularity, support for claims 17, 69, 71 and 73 of the instant application.

Thus, claims 1, 2, 4-16 and 64-68 of the instant application have a priority date of 11/22/1996 and claims 17, 69, 71 and 73 of the instant application 09/888,164 have a priority date of 03/31/1999.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 18-23 and 72 rejected under the judicially created doctrine of double patenting over claims 1, 8 and 9 of U. S. Patent No. 5,994,517 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Claims 1, 18-23 and 72 of the instant application are drawn to a construct comprising a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P

represents a biologically stable oligomer that binds to a hepatic pathogen. The instant claims are further limited wherein the oligomer comprises a deoxyribose methylphosphonate internucleotide linkages or a combination of deoxyribose methylphosphonate/phosphodiester internucleotide linkages. The instant claims further recite the A-L moiety is YEE(ahGalNAc)3-SMCC.

Claims 1, 8 and 9 of Patent '517 are drawn to a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P broadly represents any biologically stable oligomer. The claims of Patent '517 further recite the deoxyribose oligomer comprises internucleotide linkages are selected from phosphodiester, methylphosphonate or a combination of phosphodiester, methylphosphonate internucleotide linkages.

Claims 1, 8 and 9 of Patent '517 are drawn to construct comprising the formula A-L-P wherein P broadly represents any biologically stable oligomer capable of binding to any target. Claims 1, 18-23 and 72 of the instant application are drawn to a construct comprising a homogenous conjugate wherein P represents a biologically stable oligomer that binds to a target, namely a hepatic pathogen and are therefore encompassed in the scope of claims 1, 8 and 9 of Patent '517

Thus, claims 1, 8 and 9 of Patent '517 anticipate claims 1, 18-23 and 72 of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 8, 7, 16, 68 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "said oligomer". There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites the limitation "said oligomer". There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation "said oligomer". There is insufficient antecedent basis for this limitation in the claim.

Claim 69 recites the limitation "said oligomer". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Korba et al. (U.S. Patent No. 5,646,262).

Claim 17 is drawn to an oligomer comprising SEQ ID NO: 29. Claim 69 is drawn to a pharmaceutical composition wherein said oligomer comprises SEQ ID NO: 29.

Korba et al. teach an oligomer sequence having SEQ ID NO: 29 (see column 33). Further, Korba et al. teach a pharmaceutical composition comprising an oligomer having SEQ ID NO: 29 (see column 9, lines 5-11).

Thus, Korba et al. anticipates claims 17 and 69 of the instant application.

Claims 17 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al. (U.S. Patent No. 5,985,662).

Claim 17 is drawn to an oligomer comprising SEQ ID NO: 29. Claim 69 is drawn to a pharmaceutical composition wherein said oligomer comprises SEQ ID NO: 29.

Anderson et al. teach an oligomer sequence having SEQ ID NO: 29 (see column 17). Further, Anderson et al. teach a pharmaceutical composition comprising an oligomer having SEQ ID NO: 29 (see column 8, lines 4-14).

Thus, Anderson et al. anticipates claims 17 and 69 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6-10, 14-29, 64-65, 68-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. (U.S. Patent No. 5,646,262) in view of Lin et al. (U.S. Patent No. 5,777,153) in further view of Hangeland et al. (Bioconjugate Chem. 1995, 6, 695-701).

Claims 1, 2, 4, 6-10, 14-29, 64-65, 68-73 of the instant application are drawn to a construct comprising a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P represents a biologically stable oligomer that binds to a hepatic pathogen. The instant claims further recite the pathogen is a hepatic virus, and further the hepatic virus is a hepatitis virus. The claims are further limited wherein the oligomer binds to a surface antigen of a hepatic virus wherein the hepatic virus is hepatitis B, the oligomer binds to a core antigen of said hepatic virus wherein the core antigen is S-gene or C-gene and the oligomer binds to an encapsidation sequence of said hepatic virus. The claims recite the oligomer comprises deoxyribose methylphosphonate, phosphodiester or phosphorothioate internucleotide linkages or a combination of internucleotide linkages. The claims further recite the oligomer comprises 2'-O-methylribose methylphosphonate, phosphorothioate or phosphodiester linkages. The instant claims are further limited wherein the oligomer comprises SEQ ID NO. 29, the A-L moiety is YEE(ahGalNAc)$_3$-SMCC or the construct comprises YEE(ahGalNAc)$_3$-SMCC-SEQ ID NO: 29 and further the oligomer is a pharmaceutical composition comprising SEQ ID NO. 29 or YEE(ahGalNAc)$_3$-SMCC-SEQ ID NO: 29.

Korba et al. teach an oligomer that binds to a surface antigen of a hepatic virus wherein the hepatic virus is hepatitis B, the oligomer binds to a core antigen of said hepatic virus wherein

the core antigen is S-gene or C-gene, the oligomer binds to an encapsidation sequence of said hepatic virus or the oligomer binds to a preS1 open reading frame (see column 7, lines 49-65 and column 8, lines 1-26). Korba et al. further teach the oligomer comprises deoxyribose methylphosphonate, phosphodiester or phosphorothioate internucleotide linkages or a combination of internucleotide linkages (see column 6, lines 56-57 and column 7, lines 5-13). Korba et al. also teach the oligomer having SEQ ID NO: 29 and further Korba et al. teach a pharmaceutical composition comprising SEQ ID NO: 29 (see column 9, lines 4-8). Korba et al. does not teach the oligomer comprises 2'-O-methylribose methylphosphonate, phosphorothioate or phosphodiester linkages or the oligomer is conjugated to a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC.

Lin et al. teach an oligomer comprising 2'-O-methylribose linkages (see column 11, lines 5-10).

Hangeland et al. teach conjugation of a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC to an oligomer (seepage 695, column 2).

It would have been obvious to one of ordinary skill in the art to modify the oligomer SEQ ID NO: 29, taught by Korba et al., with the 2'-O-methylribose phosphodiester linkages taught by Lin et al. Further, it would have been obvious to one of ordinary skill in the art to conjugate the modified oligomer SEQ ID NO: 29, as taught by Korba et al. and Lin et al. to a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al.

One would have been motivated to incorporate the modifications, as taught by Lin et al. into the oligomer SEQ ID NO: 29 taught by Korba et al. because such modified oligomers increase an oligomer's cellular uptake, target affinity and resistance to degradation. Further, one

would have been motivated to conjugate a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al. onto the oligomer SEQ ID NO: 29, taught by Korba et al., because the bifunctional linker SMCC is metabolically stable and further the hepatic ligand YEE(ahGalNAc)$_3$ increases the specificity of the construct to a hepatic receptor thereby increasing the cellular uptake.

Finally, one would have had a reasonable expectation of success at making a construct comprising a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC to an oligomer that specifically binds to a hepatic receptor because Hangeland et al. specifically teach a conjugate that specifically targets hepatic receptors and increases cellular uptake of the construct (see page 699, columns 1 and 2).

Thus, in absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 4, 7, 11, 12, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blumenfeld et al. (U.S. Patent No. 6,369,038) in view of Hangeland et al. (Bioconjugate Chem. 1995, 6, 695-701).

Claims 1, 4, 7, 11, 12, 66 and 67 of the instant application are drawn to a construct comprising a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P represents a biologically stable oligomer that binds to a hepatic pathogen. The instant claims recite the pathogen is a hepatic virus wherein the virus is hepatitis C or hepatitis D and further wherein the oligomer is a pharmaceutical composition.

Blumenfeld et al. teach an oligomer that can be targeted to a Hepatitis C and Hepatitis D virus (see column 16, lines 20-25). Further, Blumenfeld et al. teach a pharmaceutical composition (see column 16, lines 44-50). Blumenfeld et al. does not teach an oligomer conjugated to a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC.

Hangeland et al. teach conjugation of a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC to an oligomer (see page 695, column 2).

It would have been obvious to one of ordinary skill in the art to conjugate the oligomer, as taught by Blumenfeld et al. to a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al.

One would have been motivated to conjugate a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al. onto the oligomer taught by Blumenfeld et al., because the bifunctional linker SMCC is metabolically stable and further the hepatic ligand YEE(ahGalNAc)$_3$ increases the specificity of the construct to the liver.

Finally, one would have had a reasonable expectation of success at making a construct comprising a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC and conjugate to an oligomer that specifically binds to a hepatic receptor because Hangeland et al. specifically teach a conjugate that specifically targets hepatic receptors and increases cellular uptake of the construct (see page 699, columns 1 and 2).

Thus, in absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 5 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (U.S. Patent No. 5,591,721) in view of Hangeland et al. (Bioconjugate Chem. 1995(6) 695-701).

Claims 1, 5 and 13 of the instant application are drawn to a construct comprising a homogenous conjugate of formula A-L-P wherein A represents a hepatic ligand that specifically binds to a hepatic receptor, L represents a bifunctional linker that is covalently linked to A and P represents a biologically stable oligomer that binds to a hepatic pathogen. The instant claims further recite the pathogen is a liver parasite and further the liver parasite is plasmodium for malaria.

Agrawal et al. teach an oligomer that is targeted to a liver parasite wherein the parasite is plasmodium for malaria (see column 9, lines 30-40). Agrawal et al. does not teach an oligomer conjugated to a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC.

Hangeland et al. teach conjugation of a hepatic ligand and a bifunctional linker YEE(ahGalNAc)$_3$-SMCC to an oligomer (seepage 695, column 2).

It would have been obvious to one of ordinary skill in the art to conjugate the oligomer, as taught by Agrawal et al. to a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al.

One would have been motivated to conjugate a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC, as taught by Hangeland et al. onto the oligomer taught by Agrawal et al., because the bifunctional linker SMCC is metabolically stable and further the hepatic ligand YEE(ahGalNAc)$_3$ increases the specificity of the construct to the liver.

Finally, one would have had a reasonable expectation of success at making a construct comprising a hepatic ligand YEE(ahGalNAc)$_3$ and a bifunctional linker SMCC and conjugate to an oligomer that specifically binds to a hepatic receptor because Hangeland et al. specifically teach a conjugate that specifically targets hepatic receptors and increases cellular uptake of the conjugate(see page 699, columns 1 and 2).

Thus, in absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

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Kimberly Chong
Examiner
Art Unit 1635